SCIENTIFIC ABSTRACT

Adenocarcinoma of the prostate is the most common malignancy in men, and is the second most common cause of cancer deaths among American men. Currently it is predicted that there will be approximately 250,000 newly-diagnosed cases in the United States in 1997, with over 44,000 patients per year dying from this disease.

There is no curative therapy for prostate cancer once it has escaped the confines of the prostate capsule. Surgical therapy offers excellent chances for cure if the disease is pathologically confined to the prostate gland. Pelvic radiotherapy has varying rates of success when used in the adjuvant setting. Once prostate cancer has spread, androgen deprivation therapy is very effective in controlling symptoms from metastasis and slowing the rate of disease growth. Androgen deprivation therapy however is not curative. Due to the slow rate of prostate cancer cell reproduction, the use of cytotoxic chemotherapy is ineffective since such treatment relies on the selective killing of actively and rapidly proliferating cells.

Loss of wild-type p53 function is permissive for development of many types of human cancers. Moreover, it has been shown in both in vitro and in vivo models that the introduction and expression of wild-type p53 into p53-altered cancer cells can be effective in treating cancer by suppression of the neoplastic phenotype.

This study seeks to evaluate the safety, biological efficacy and the effect of dose of SCH 58500 treatment. SCH 58500 is a recombinant adenoviral vector containing the wild-type human p53 gene. SCH 58500 will be administered as a series of 2 intratumoral injections for the local gene therapy of adenocarcinoma tumors of the prostate. Study patients will have locally advanced or recurrent adenocarcinoma of the prostate, with evidence of p53 alteration in their tumor tissues. In vitro studies have demonstrated p53-specific anti-cancer effects of SCH 58500 on a variety of p53-altered human tumor cell lines including squamous cell carcinoma of the head and neck, colorectal, hepatocellular, non-small cell lung, breast, ovarian and prostate carcinomas.

The SCH 58500 construct is a recombinant, replication-deficient, adenovirus derived from adenovirus serotype 5 (Ad5), subgroup C. The adenoviral Ela, Elb and protein IX coding sequences are deleted and replaced with the p53 expression cassette. The deleted E1 region is necessary for viral replication. The virus is additionally deleted for 1.9 kb of DNA sequence in Early Region 3, including that sequence encoding the gp19K protein. The p53 expression cassette contains the human cytomegalovirus immediate early promoter-enhancer, the adenovirus type 2 tripartite leader sequence and a sequence encoding wild-type p53 protein. The human cytomegalovirus immediate early promoter-enhancer directs robust gene expression and the adenovirus type 2 tripartite leader sequence enhances translation efficiency. Polyadenylation is regulated by the E1b and pIX polyadenylation signal. All other regulatory elements and replication origins within SCH 58500 are endogenous to Ad5. The recombinant adenovirus is similar to other adenoviral vectors reviewed by RAC and the FDA except that it contains the additional deletion of the pIX coding sequence. The deletion in the pIX coding sequence is expected to reduce the frequency of replication competent adenovirus arising during virus production by reducing the sequence identity with the E1 sequences of the 293 production cell line.

The study design is an open-label, non-randomized, dose escalation Phase I clinical trial anticipated to involve a maximum of eighteen patients. SCH 58500 will be administered in escalating does to successive cohorts of patients until the maximum tolerated dose is determined. Local SCH 58500 therapy will be administered as a series of 2 intratumoral injections. The route of administration of SCH 58500 via intratumoral injection is designed to maximize gene therapy exposure to the malignant tumor while minimizing exposure to normal tissues. The clinical protocol is designed to monitor treatment toxicity. Another objective is to evaluate the biological efficacy, including efficiency and stability of gene transfer by analysis of tumor tissues following therapy. Clinical evidence of anti-tumor efficacy will also be collected. In addition, the safety and efficacy of different dose levels of SCH 58500 will be studied.